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A Perspective of Diverse Synthetic Approaches and Biological Applications of Vitamin K

Satyanarayana Battula

Abstract

Vitamin-K is a demanding multi-functional health product in the market and belongs to a class of isoprenoid molecules that comprises methylnaphthoquinone (MK) unit attached to an isoprene side chain. They are fat soluble and differ in the extent of side chain & obtained in the nature as vitamin K₁ (phyloquinone), menaquinone/vitamin K₂, and other lipoquinones. Owing to their owned polyprenyl side chain, they are hydrophobic/lipophilic in nature. Generally, the synthesis of vitamin K and its variants suffers with isomerization (for example 11 isomers were identified for cis/trans MK-7). Naturally, in bio-systems vitamin K produces through shikimic acid pathway and terpene biosynthetic pathway for the synthesis of menaquinone part & prenyl side chain parts respectively. Menadione or its auxiliaries are commonly being used as substrates to the synthesis of vitamin K variants through the involvement of condensation reactions, Friedel-Craft alkylation's, Claisen rearrangement, Diels-Alder reactions and others. Importantly, organometallic reagents, such as Grignard, Gilman, organotelluride and other reagents could be the promising and consistent choice of substrate to the synthesis of various vitamin K's. Vitamin K is well known for blood coagulation. As an antihemorrhagic vitamin, it's also being the current interest for the treatment of bone and vascular diseases. In addition, vitamin k is indispensable for the activation of vitamin K dependent (VKD) proteins and that are present almost in all tissues and responsible for hemostasis, bone mineralization, arterial calcification, apoptosis, phagocytosis, growth control, chemotaxis, and signal transduction. This chapter summarizes various synthetic approaches of vitamin K & derivatives and their biological functions.

Keywords: Vitamin K, Menaquinones, Biosynthesis, Synthetic auxiliaries, Organometallic reagents, MenJ, Vascular diseases, diabetes

1. Introduction

Vitamin K is a family of natural products, comprises vitamin K₁ (phyloquinone), vitamin K₂ (methylnaphthoquinones/menaquinones-MK) and vitamin K₃ (menadione). These are structurally methylated naphthoquinones possess isoprene side chain (vitamin K₁ & vitamin K₂) and they vary in the extent of isoprene side chain, in terms of number of isoprene units and its level of saturation [1–5]. However, these structural changes are apparently simple, but needs exist in its specific stereochemistry to exhibit their biological functions. These are

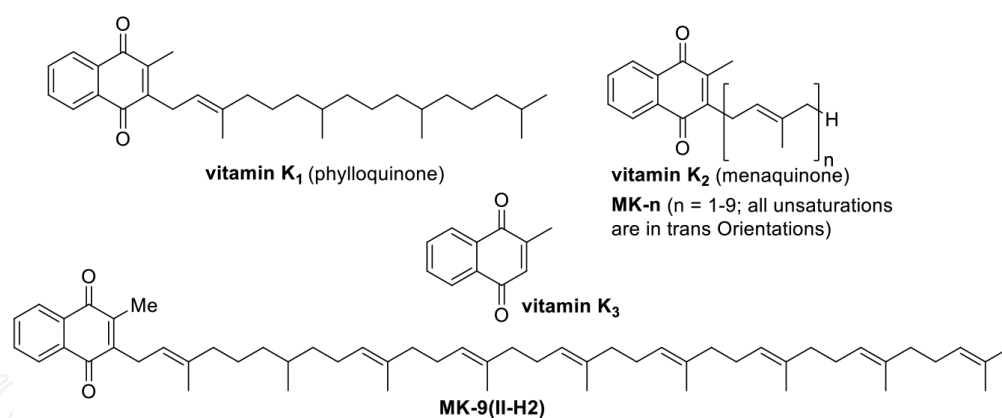


Figure 1.
Structures of vitamin K.

the fat-soluble compounds and pertains to a class of lipoquinones [6]. Vitamin K₂ are varied on the basis of number of isoprene units present in the side chain and they denoted as MK-n (n – number of isoprene units; **Figure 1**). The vitamin K₂ if contains saturated isoprene units referred as MK-n(m-H₂), wherein m is a roman numeral represents isoprene unit number in the side chain which underwent reduction. Among the two natural forms of vitamin K, vitamin K₁ presents in green leafy vegetables, for example, kale, collard greens, turnip greens, iceberg lettuce, broccoli, spinach, and brussels sprouts. The Vitamin K₂ presents naturally in eggs, meat, fermented foods (natto, cheese, yogurt and sauerkraut) also present in bacteria, for example, MK-9 is found in mycobacterium with nine isoprene units and also its reduced derivative at second isoprene unit MK-9(II-H₂) could be active as electron transport agent in [3, 7]. In humans, these menaquinones display several biological properties, including facilitating blood coagulation [8, 9]. In bacteria, these molecules assisting the synthesis of ATP through transport of electrons between the membrane-bound protein complexes and thus acting as electron acceptors and donors in the respiratory electron transport [10, 11]. Vitamin K and its analogues could not synthesize by mankind/animals. So, its required to supply an adequate amount through the dietary sources.

2. Vitamin K biosynthesis

Naturally, bacteria producing different variants of vitamin K. Among the aerobic bacteria, most of its Gram-negative bacteria contain ubiquinone as the sole quinone, whereas the menaquinone is the only quinone presents in aerobic Gram-positive bacteria. But, in the case of anaerobic bacteria, irrespective of whether it is Gram-positive or Gram-negative, it produces benzoquinones (ubiquinone), naphthoquinones (menaquinones; MK-n), demethylmenaquinones (DMK-n) [12]. The Gram-negative bacteria, such as, *Escherichia coli* and *Salmonella enterica* serovar Typhimurium possesses these isoprenoid quinone molecules, viz., benzoquinones and naphthoquinone. In *E. coli*, it contains MK-8 and DMK-8 as the major naphthoquinones & in addition, it also comprises MK-6, MK-7, MK-9 and DMK-9 in minor quantities (**Figure 2**) [13].

These menaquinones have prenyl side chains with all-*trans* configurations. MK-10 and MK-11 are the isoforms of vitamin K₂ and are produced from bacteroides. MK-7 produced from veillonella sp. and MK-6 is from *Eubacterium lentum*. The menaquinone nucleus of vitamin k was being synthesized in the nature by shikimic acid pathway and that can be described as a “metabolic tree with many branches and was derived from isochorismate via chorismate. The prenyl side chains in the

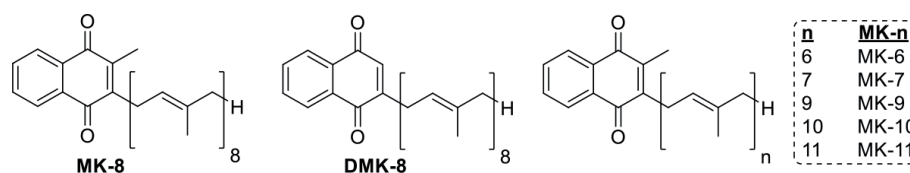


Figure 2.
 Structures of vitamin K₂ (MK-*n*) & DMK-*n*.

molecules are synthesized before its incorporation into the final compound through the terpene biosynthetic pathway and are derived from prenyl diphosphate, and the methyl groups in the vitamin K are derived from S-adenosylmethionine. The menaquinone biosynthesis involves the introduction of prenyl side chain, and that is accompanied by the loss of the carboxyl group and then occurred the C-methylation on quinone moiety [12].

Cox and Gibson discovered in 1964, shikimate was present in menaquinone of *E. coli*, and thus it could be the first report as an evidence to shikimate pathway to the synthesis of menaquinones. The chemical degradation reaction of labeled isolated MK-8 displayed that all the radioactivity is associated with degraded product phthalic anhydride. It indicated that the benzene ring of naphthoquinone part in the vitamin K₂ was procured from shikimate in the bacteria [14]. It was further established that, the menaquinone biosynthesis was started with shikimate as a starting precursor and it was confirmed from a complete degradation study of the menaquinone which was constructed by the labeled shikimate molecule. This study was indicated that all the seven carbon atoms of shikimate were incorporated in the naphthoquinone part of menaquinone [15], and the remaining 3 carbon atoms were revealed to be derived from the 2-ketoglutarate (**Figure 3**) [16, 17].

Shikimate pathway for the synthesis of menaquinones is presented in **Figure 4**. Shikimate was proposed to converted initially into chorismate before its incorporation into menaquinone [15]. In *E. coli*, isochorismate formation occurred from chorismate and it was mediated by isochorismate synthase (encoded as *MenF*). The source of the hydroxyl group in the isochorismate could be either molecular oxygen (occur in aerobic organism), or intramolecular -OH group transfer or from the solvent water [18]. Later, it was postulated that, the 2-ketoglutarate gives succinic semialdehyde anion of TPP through a TPP-dependent decarboxylation and that catalyzes by 2-ketoglutarate decarboxylase (KDC) [16, 19]. Subsequently, this anion reacts with isochorismate and produces 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate (SHCHC). MenD protein was found that it incorporated both SHCHC synthase & KDC activities and was encoded with a single gene [20]. Further studies

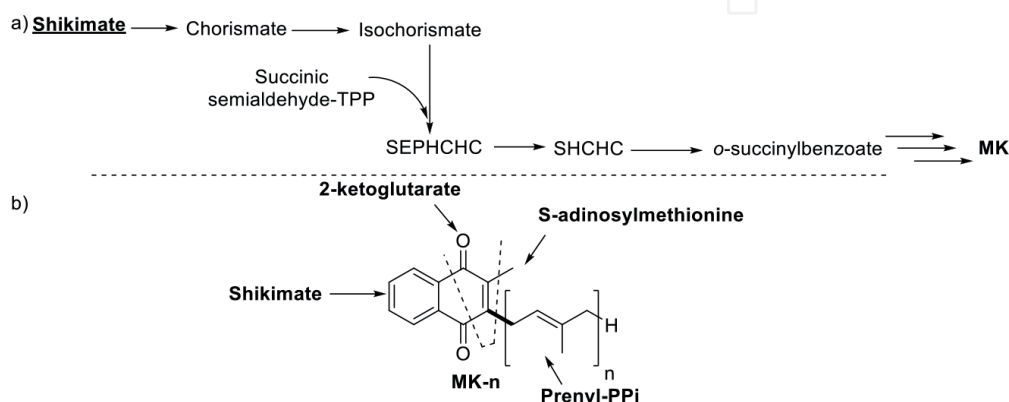


Figure 3.
 a) Sequential formations in the biosynthesis of menaquinones; b) the preliminary precursors in MK-*n* biosynthesis.

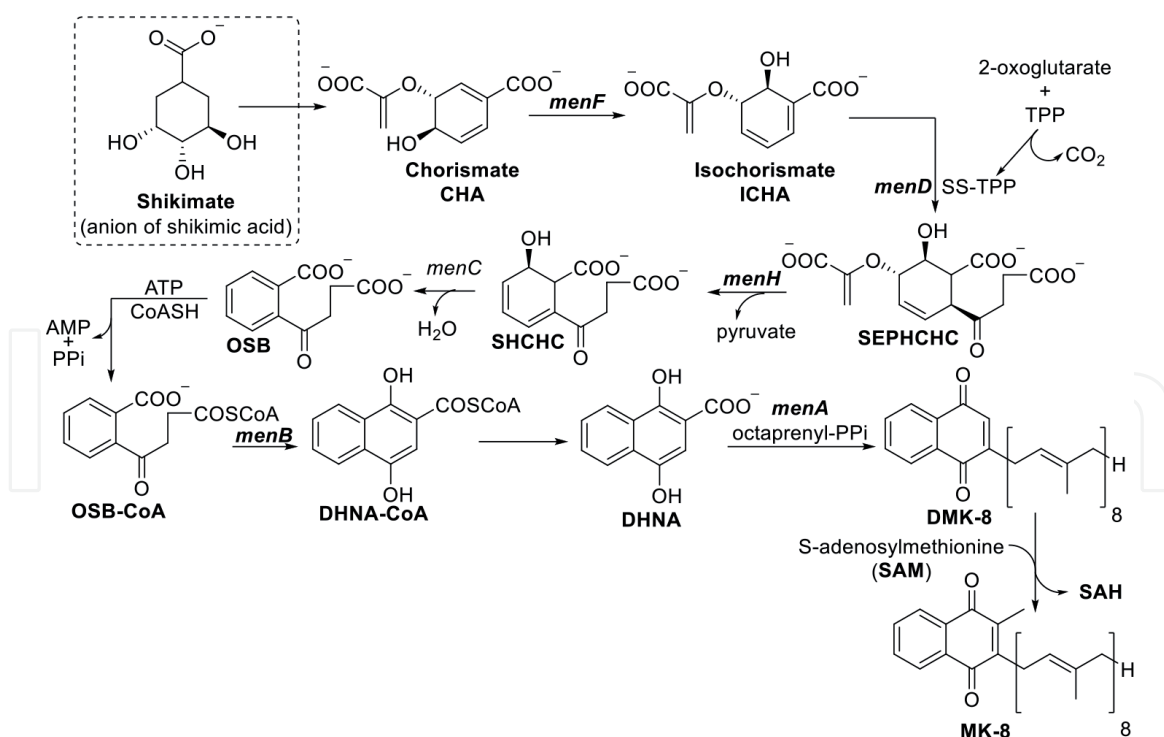


Figure 4.
Biosynthetic pathway of Menaquinone molecules.

shown that, SHCHC formation is proceeded through the formation of 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylate (SEPHCHC) and was catalyzed by SEPHCHC synthase [21]. As this SEPHCHC compound unstable, under mild basic conditions, it converts to SHCHC spontaneously [22]. This *in vivo* conversion was carried out by SHCHC synthase encoded by *menH* gene (Ser-His-Asp; a catalytic triad) [23]. Later, the removal of water molecule from SHCHC to produces benzenoid compound, *o*-succinylbenzoate (OSB) and this transformation was carried out by OSB synthase & encoded as *menC* [24]. Bryant and Bentley described the transformation of OSB in to the 1,4-dihydroxy-2-naphthoate (DHNA) [25]. It was derived by ATP and CoA, so that OSB-CoA could be the proposed intermediate driven by the *menE* gene. Two enzymatic activities are worked on this conversion, viz., OSB-CoA synthetase and DHNA synthase. Due to the un-stability of OSB-CoA, as an intermediate it was converted to DHNA through the involvement of DHNA-CoA [26]. Further Bentley was shown that the conversion of DHNA to DMK was happened in the extracts of *E. coli* [27]. The transformation of DHNA to DMK occurs through the exchange of carboxyl with isoprenoid side chain. Both these processes, prenylation and decarboxylation perhaps occur at a single reactive center [28]. The *MenA* enzyme has carried out this process with octaprenyl PPi [29, 30]. Finally, the conversion of DMK to MK was happened by a methyltransferase, and that uses *S*-adenosylmethionine as the methyl donor [25, 31]. Moreover, Meganathan and group was extensively studied and reviewed detailed mechanistic studies for the shikimate pathway mechanism for the biosynthesis of vitamin K₂ [12, 32].

3. Various synthetic approaches to vitamin K

In 1939, Fieser [33], Binkley [34], and Almquist [35] were reported initially the synthesis of vitamin K₁ independently. The condensation reaction of either menadione/2-methyl-1,4-naphthohydroquinone with natural phytol in the presence of oxalic acid or zinc dust in acetic acid produce vitamin K₁ (Figure 5).

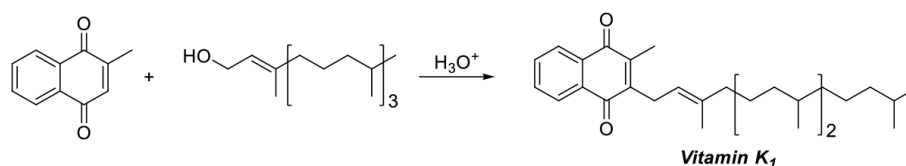


Figure 5.
 The first synthesis of vitamin K₁.

The initial synthetic approaches were generally proceeding through the usage of Friedel-Craft alkylation's for introducing the side chains through its coupling to menadions, which led to the generation of mixture of isomers at the Δ_2 position and produced *E*-isomer as the major (90%). Later it was developed by Lindlar to accomplish the complete retention of configuration of the side chain by taking the use of menadiol ester (menadiol 1-benzoate) in the catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ instead of menadiol [36]. But the reaction suffers with the allylic alcohol instability to the acidic reaction conditions. Later days, the synthesis of vitamin K was achieved by coupling reactions of protected menaquinones with side chains, the protection is depending on the nature of the substrates and deprotection protocols. Transition metals (Ni [37], Ag [38]) show huge applicability in these coupling reactions to the synthesis of vitamin K. Furthermore, organometallics did this synthesis through the reactions of their metallonaphthalenes with corresponding side chain halides. Among, Grignard reagents were given excellent reactions with 99% stereo retention of the *E*-configuration. By using this magnesium organometallics Evans and Hoffman did a regiospecific isoprenylation of naphthoquinones to the vitamin K [39]. In this reaction, trimethylsilyl cyanide (TMSCN) added 2-methoxy-3-methyl-1,4-naphthoquinone gave the protected quinone wherein cyanide was acted as a catalyst. This protected quinone underwent reaction with prenyl magnesium bromide followed by a Cope rearrangement to obtained the protected MK-1. It's deprotection was later performed with AgF, consequently it afforded the MK-1 (**Figure 6**).

In addition, Organocuprates were also being used to the synthesis of vitamins K's. Menaquinone and phyloquinone are synthesized by Chenard group, from the reaction of Gilman based bisketals of quinone substrate with allyl halides and it afforded high yields and good stereoselectivity at the Δ_2 position of the vitamin K (**Figure 7**). The quinone bromide underwent metalation to produce the corresponding cuprate, and its reactivity was varied with different electrophilic substrates (RX). Among the tested electrophilic substrates, if the electrophilic group is small enough (allyl bromide) then the two alkyl groups of cuprate reagent were being used being transferred in the reaction. If the reaction with bulkier electrophilic halide (for example benzyl chloride/bromide, cyclohexanecarbonyl acid chloride), cuprate can transform only one alkyl group [40]. Syper group synthesized protected forms of MK-1 and MK-2 in appreciable yields through the coupling reaction of prenyl bromide and geranyl bromide with 2-bromo-3-methyl-1,4-dimethoxynaphthalene [41]. Generally, these organometallics (Grignard reagents, organocuprates and organolithiums) mediated synthesis of vitamin K required the usage of protected quinones to avoid the side reactions. Unprotected quinones could also give the vitamin k synthesis through their direct coupling with organostannates [42] and organosilanes [43].

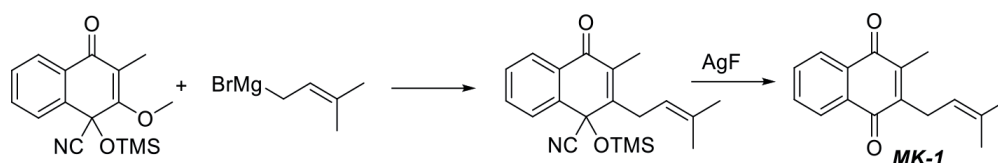


Figure 6.
 Grignard reagent mediated synthesis of MK-1.

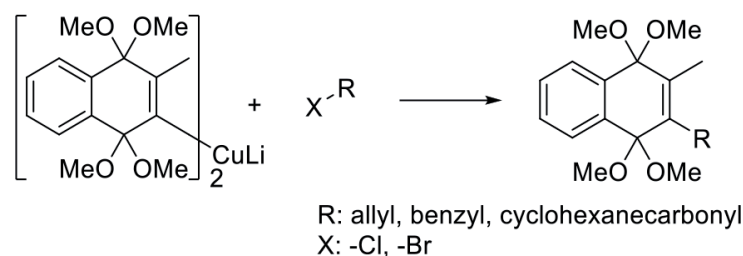


Figure 7.
Menaquinone analogs synthesized by organocuprates.

Tso and group developed an efficient and conceptually distinguished one-pot protocol to the synthesis of vitamin K, wherein the 3-substituted isobenzofuranone was treated with a base, the generated quinone methide which underwent an anionic [4 + 2] cycloaddition reaction with the alkenyl phenyl-sulfone (dienophile) and that was being synthesized from the corresponding allyl phenylsulfone and various prenyl bromide (RBr). Finally, the vitamin K was produced by the elimination of sulfone from the intermediate. This method was very compatible to the synthesis of phyloquinone and different menaquinone variants MK-1, MK-2 and MK-9 about 60–65% yields (**Figure 8**) [44].

In 2015, Mal et al., extended this protocol to the synthesis of menadione derivatives (MK-n molecules) by a base mediated reaction of 3-substituted phthalide with methyl methacrylate [45]. The yield of the reaction was verified in this reaction with various leaving groups, such as - methoxy, phenyl sulfonyl, isonitrile, thiophenyl, and nitrile. The nitrile leaving group in the substrate was found to be the best suitable one for the reaction. The 3-nitrilephthalide is to be a menadione auxiliary to the reaction of MK-n variants (**Figure 9**). The reaction was proceeds through a base mediated anionic driven annulation of 3-nucleofugal phthalides with α -alkyl/aryl acrylates followed by demethoxycarbonylation. If the polyprenyl acrylates are to be the substrates, then various analogs of menadione were being produced (MK-n).

Side chain functionalization methods were also being developed to the synthesis of vitamin K analogs. These derivatized vitamin K are received a great deal of interest to reveal the structure activity relationship studies (SAR). These analogs were also proved to be as inhibitors of vitamin K dependent carboxylase and vitamin K epoxide reductase [46]. The side chain stereochemistry is very essential to exhibit the biological activity, as the *E*-isomers of these vitamins are producing activity and the isomers with *Z*-configuration could lead to loss of their activity. The longer chain in the menaquinones causes to account lower biological activities due to their hydrophobicity [47].

Snyder and group during their sustained efforts to retain the stereochemistry of α -isoprene double bond, they introduced the alkylation of enolates to the synthesis of vitamin K [38]. The synthesis involves the interaction of nucleophilic aromatic component to the receptive prenyl component through its enolized nucleophile.

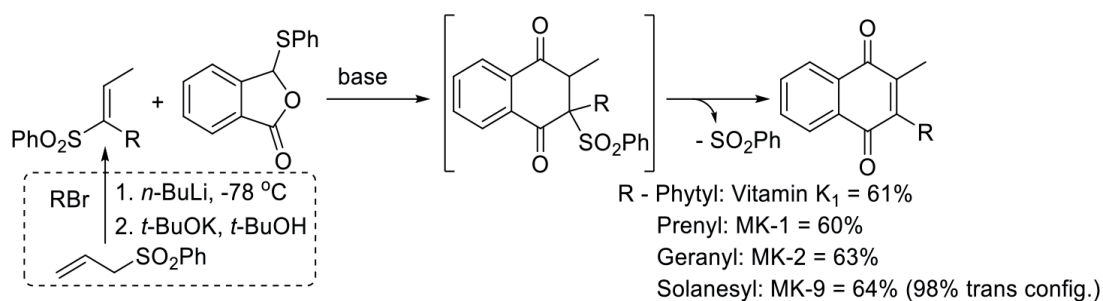


Figure 8.
Methide annulation to a one-pot synthesis of vitamin K.

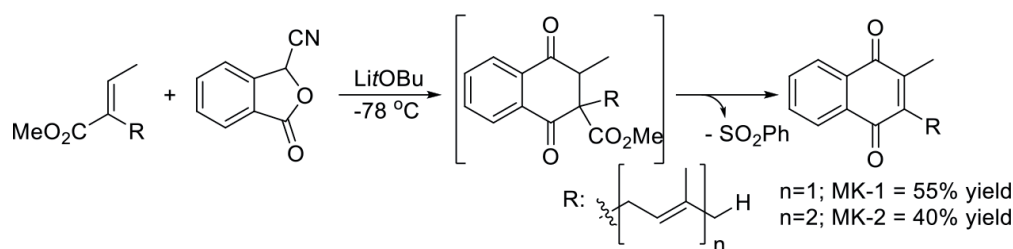


Figure 9.
 Anionic annulation of 3-nucleofugal phthalides to the synthesis of vitamin K.

Initially, the menadiol forms its potassium salt in presence of either potassium hydride or potassium methoxide and then underwent prenylation through the enolate alkylation, later in presence of silver oxide get oxidized into prenyl fragment substituted menadione (MK-2 and MK-9) and was shown in **Figure 10**.

However, these enolyte alkylations were successful but not very practical. To accomplish the practical methods, Snyder group developed transmetallation method for the synthesis of vitamin K [38]. Lithium, magnesium and copper had used to convert 2-bromomenadiol to its corresponding metallo derivative. As an electrophilic partner authors chosen initially aldehydes, but aldehydes are unsuccessful as the resultant alcohol functionality removal afforded either vinyl alkenes or α -isoprene double bond isomerization. Later, the prenyl halides are found to be the appropriate substrates of electrophiles for these transformations. Primarily, reactions were performed to evaluate the stereoretention of the α -isoprene double bond in each of the 2-metallo derivatives. As per their expectation, all these metallo derivatives could not affect the configuration of the isoprene component of the vitamins. It was found that, organo magnesium reagents are more efficient than organocuprates and that in turn efficient than organo lithium reagents. Among the prenyl halides, prenyl bromides are generated excellent yields of menaquinone analogs (**Figure 11**). The coupling of 2-magnesio or 2-cupro-3-methyl-1,4-dimethoxynaphthalene with geranyl bromide produced in >90% yield. In this method, MK-9 was obtained in 73% yield by treating solanesyl bromide with menadiol.

In the various synthetic strategies to the vitamin K in the literature, Friedel-Crafts alkylation protocol of menadiols is the most popular across the literature. Hirschmann group developed a method wherein the applicability of various Lewis and Bronsted-Lowry acids were being used for the synthesis of vitamin K₁ [48]. Monoacetate of menadiol substrate was treated with phytol in presence of various acids. Among, the acids, BF₃.Et₂O afforded appreciable yields (67%) rather others being tested KHSO₄, oxalic acid and Duolite C-60. After Friedel-Crafts alkylation, finally, the acetate group was removed by the treatment with Ag₂O (**Figure 12**).

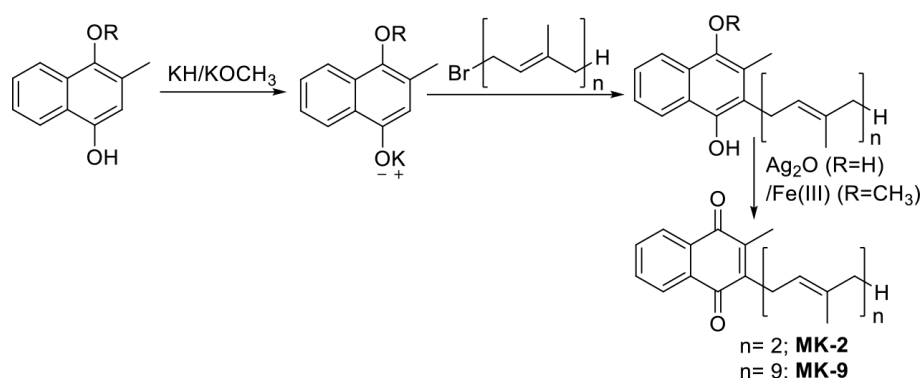


Figure 10.
 Enolate alkylation of menadiols to MK-n synthesis.

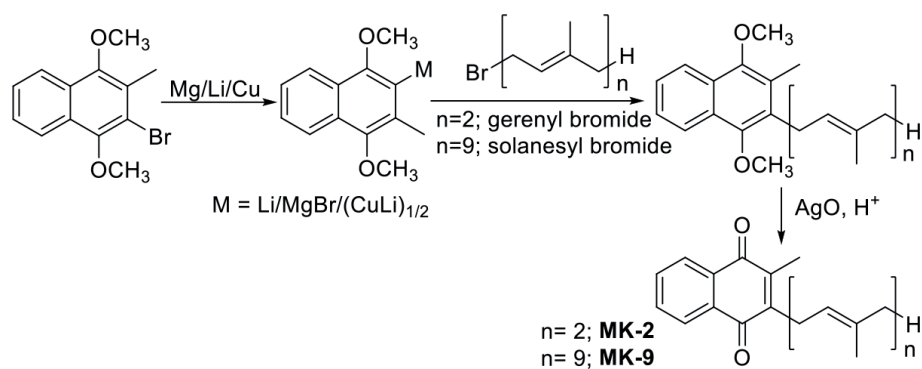


Figure 11.
Efficient transmetalation reaction to menaquinones.

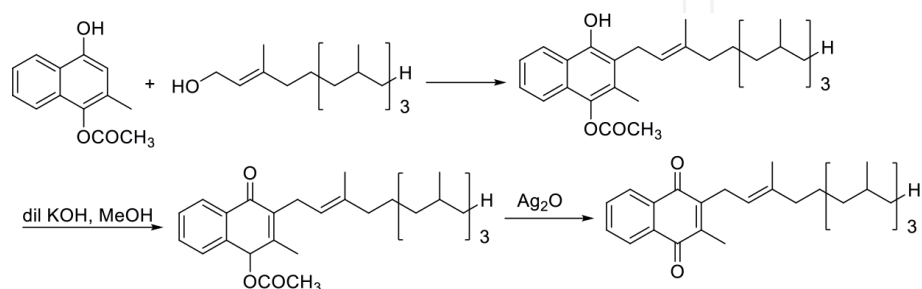


Figure 12.
Application of Friedel-Crafts alkylation to the synthesis of vitamin K₁.

Later, in 1990 Schmid and group enriched the yield of the reaction by treating the reaction of menadiol monoacetate with phytyl chloride in presence of a base potassium carbonate, wherein O-phytylated derivative had obtained. This was further undergoing Claisen rearrangement under acidic treatment with catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to C-phytylated product in 76–80% yield and the ratio of the configurations of E and Z isomers was found to be 97:3. The deacetylation was carried out in basic medium (**Figure 13**). Vitamin K₁ obtained in this procedure is to be 96.5% and with E-configuration, Z -configuration compound was with very low yield (3%) [49].

Apart from the electrophilic side chain attachment to the menadiones, radicals also found to do the same work to make the synthesis of vitamin K. Jacobson and coworkers in 1972, developed a method to the alkylation of quinones by the use of radicals and that were produced by metal/persulphate catalyzed decarboxylation of the corresponding carboxylic acid. 4-Methyl-3-pentenoic acid produced the 3,3-dimethylallyl radical while in presence of AgNO_3 , $(\text{NH}_4)_2\text{S}_2\text{O}_8$. Initially Ag^+ is reacted with $\text{S}_2\text{O}_8^{2-}$ to form Ag^{+2} and which abstract an electron from carboxylic

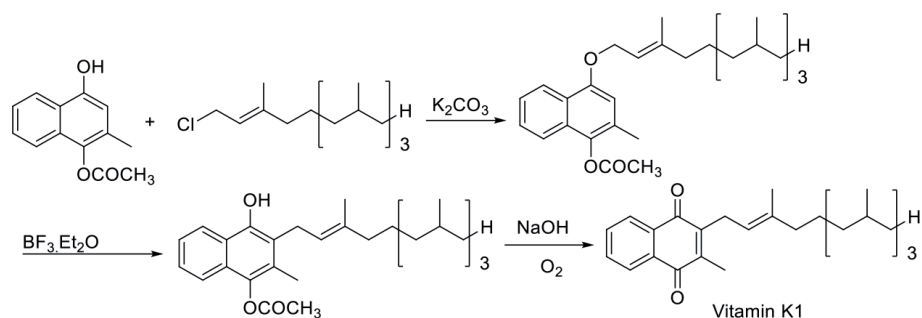


Figure 13.
 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyzed Claisen rearrangement to vitamin K₁.

acid to produce allyl radical by the ejection of CO₂. This allyl radical resonates and unexpectedly less stable isoform γ,γ -dimethylallylquinone was given the product instead to α,α -dimethylallylquinone (**Figure 14**). By this procedure MK-1 obtained in 70% yield as a γ,γ -dimethylallylquinone as to hold a stable alkene [50].

Later, Yamago et al., found the applicability of organotellurium compounds to the radical coupling reactions with a variety of quinone substrates [51]. This method could offer the general protocol to the synthesis of polyprenyl menadiones with complete retention of stereochemistry. Organotellurides were prepared by SmI₂ mediated coupling reaction of its corresponding bromides with ditolyl ditelluride (Tol)₂Te₂. This telluride later produced prenyl radical under photo/thermal energy source and that interact with menadione to produce respective MK-n related to the length of the prenyl side chain. While geranyl tolyl telluride (73:23 mixture of the trans and cis isomers) react with 2-methyl-1,4-naphthoquinone to produce MK-2 in moderate yield. The stereochemistry of the product (7:3) informed that the reaction gave the retention of stereochemistry of organic telluride in to the product (**Figure 15**).

Diels-Alder reactions were useful to construct naphthoquinone structural unit, as Rüttimann and group being used this concept to develop protocol for the synthesis of vitamin K₁. The reaction of dihydroisobenzofurane was performed with activated alkyne dienophile (96:4 E/Z) at 80°C overnight to form the trimethyl silyl ether of Diels-Alder adduct and its reaction further carried out with methanol and then methyl group at C₂ position is achieved through the reduction of ester with bis(2-methoxyethoxy)aluminum hydride followed by air oxidation produces vitamin K in moderate yield (**Figure 16a**, 50%) [52]. During the reaction the isoprene double bond configuration was not altered. Later, he developed the reaction by taking an auxiliary to support the reaction. Rüttimann along with Büchi had taken cyclopentadiene as a substrate auxiliary and its reaction was carried out with menadione to generate Diels-Alder adduct (**Figure 16b**). Prenylation/ alkylation at C3 position of Diels-Alder adduct was performed under strong base (KOtBu, NaNH₂, KNH₂).

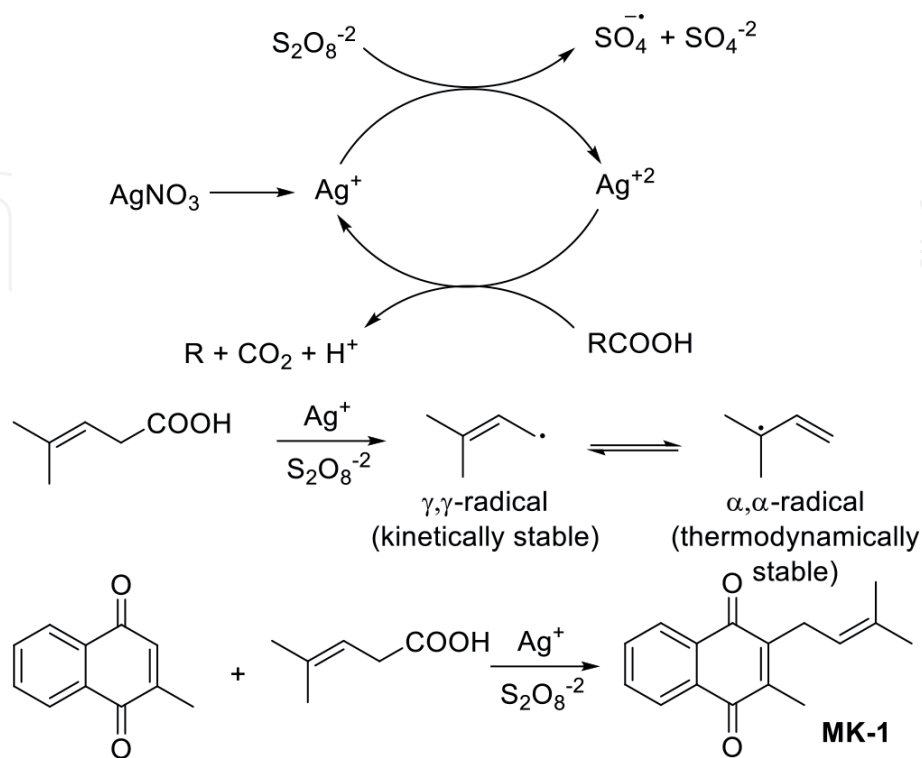


Figure 14.
 $\text{Ag}^+/\text{S}_2\text{O}_8^{2-}$ mediated radical directed synthesis to MK-1.

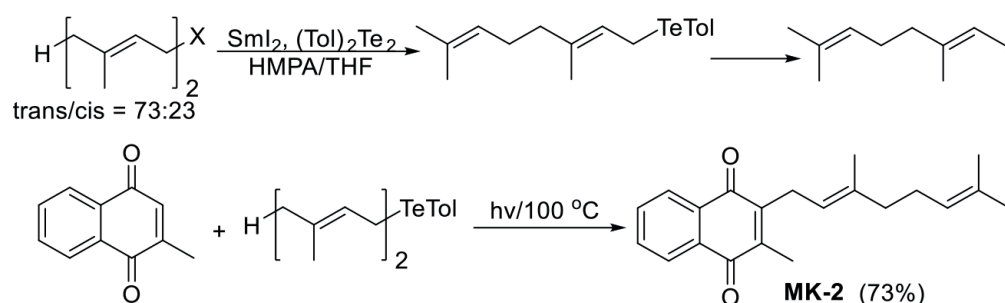


Figure 15.
Organo telluride mediated radical coupling synthesis to vitamin K.

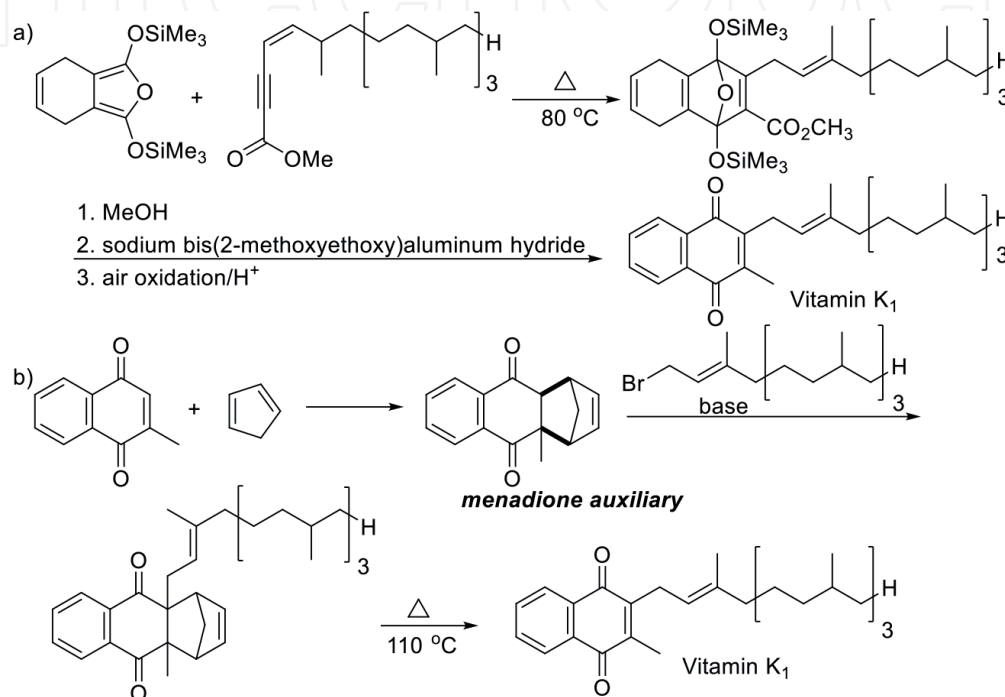


Figure 16.
a) Diels-Alder reaction mediated synthesis to vitamin K₁; b) Cyclopentadiene auxiliary driven synthesis to vitamin K₁.

Inspired by menadione auxiliary applicability in the synthesis of vitamin K₁, Battula, S., and group, thought to introduce the polyisoprenyl side chain on to the menadione to synthesis MK-n variants. This menadione surrogate was utilized to the synthesis of MK-9 in one pot protocol. The reaction of 1-Chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez reagent) with solanesol and Diels-Alder adduct of menadione was produced MK-9, wherein solanesol chlorination was happened initially to produce solanesyl chloride and that was treated with menadione auxiliary in presence of a strong base KO^tBu. Finally, the reaction was treated with acetic acid followed by tributylmethylammonium bromide to eliminate the by-products. In this procedure, MK-9 was obtained in 77% yield (**Figure 17**). The reaction with bromine based Ghosez reagent was generated MK-9 with 65% yield, as its higher leaving group ability than chloride facilitates to the formation of side reactions like S_n^{2'} reaction and cyclic reactions [53].

In the view of the requirement of MK-7 owing to its high lipophilicity and good bioavailability in small intestines and about 3 days half-life than compare to other menaquinones and ubiquinone, Aneta et al. in 2016 developed a practical synthetic strategy for vitamin K₂ (MK-7) [54]. The synthesis of MK-7 was achieved in all the *trans* forms in the side chain through 1 + 6 convergent synthetic protocol and that involves condensation of menadione monoprenyl fragment with all-*trans* hexaprenyl

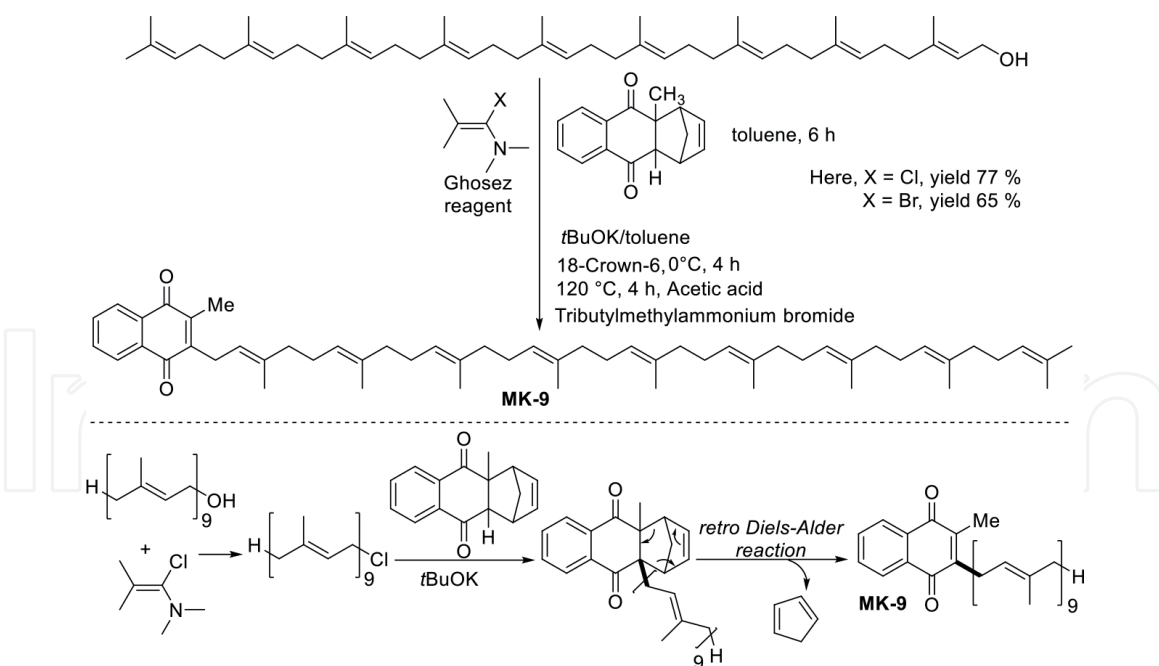


Figure 17.
 One-pot synthesis to MK-9.

bromide fragment. All-*trans* hexaprenyl bromide fragment was being synthesized from two tryprenyl molecule, i.e., *trans,trans*-farnesol. This method also implemented to the industrial level synthesis of MK-7 to compensate the need of dietary supplement as it affords high purity of the final compound MK-7 (**Figure 18**).

Among the two coupling components, hexaprenyl fragment was obtained from commercially available *trans,trans* farnesol & *trans,trans* farnesyl bromide by the following synthetic steps. The other substrate monoprenyl 1,4-dimethoxy naphthalene was produced from menadione and phenylsulfonyl, hydroxy isoprene compounds. Both these substrates were coupled in the presence of strong base

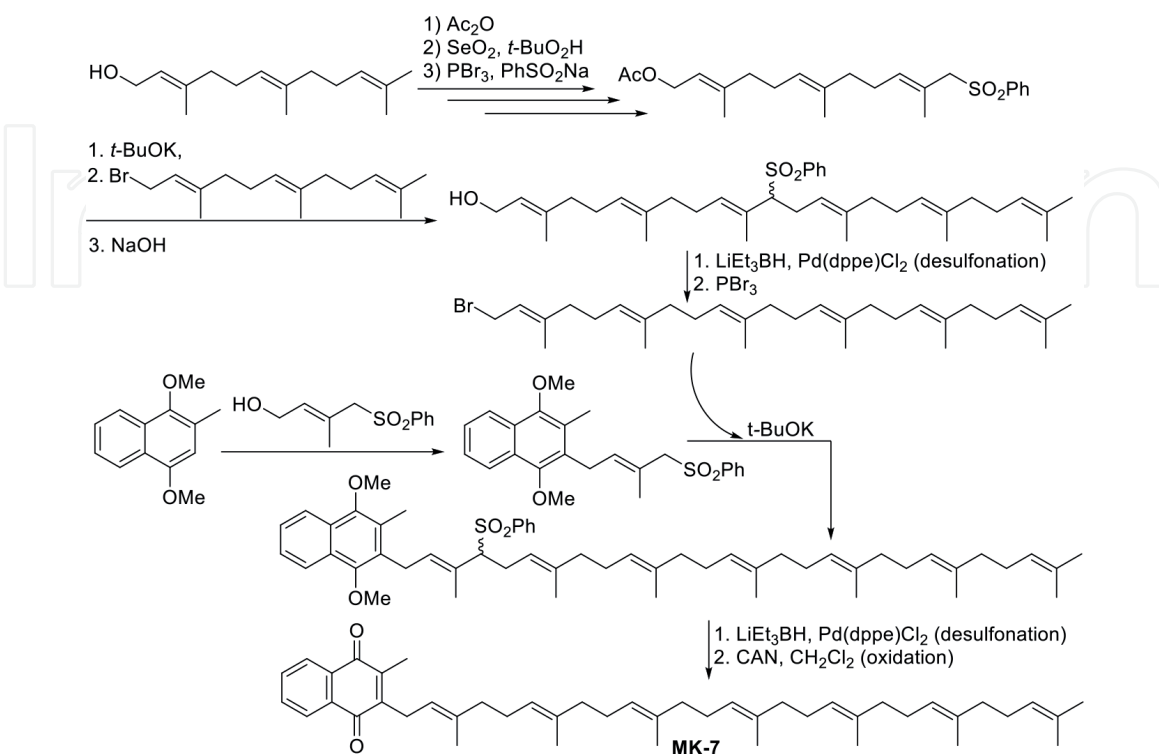


Figure 18.
 Convergent synthesis of MK-7.

t-BuOK, followed by the desulfonation at the side chain was performed by LiEt_3BH in presence of $\text{Pd}(\text{dppe})\text{Cl}_2$. Later, the 1,4-dimethoxy naphthalene was oxidized with CAN. This “1 + 6” convergent synthetic strategy is based on the condensation of monoprenyl derivative of menadione with hexaprenyl molecule was produced MK-7 in all trans stereo isoforms of side chain.

As this method was convenient in the availability of starting substrates and perfect stereochemistry of the product, Battula, S., and group developed the similar convergent synthetic strategy to MK-6 as well (vitamin K_2 variant) in all the trans forms of side chain through “1+5 convergent synthetic approach” of pentaprenyl chloride with monoprenyl menadione derivative [53]. During this survey, authors found that bromo based polyprenyl substrate was produced $\text{S}_{\text{n}}^{2'}$ side reaction product along with the main product. In addition, during LiEt_3BH mediated desulfonation, it evolves a by-product Et_3B and that leads to give cyclized side product. These limitations in the synthetic strategy interrupt the purification processes and effect the yield of the final product MK-6. To minimize these limitations, the reaction strategy was incorporated less efficient leaving group/ more efficient nucleophile (Cl) in the polyprenyl derivative to eliminate all $\text{S}_{\text{n}}^{2'}$ side reactions and thus enhance the yield and purity of the product. Further in the reaction sequence, to prevent the side reactions due to the Et_3B by product (from the desulfonation reaction), the corresponding desulfonation reaction was treated with acetic acid to quench the by-product Et_3B . Authors were applied the same strategy to the one-pot synthetic protocol to MK-9 (vitamin K_2 variant). The reaction of phenyl sulfone derivative of monoprenyl menadiol with pentaprenyl chloride was occurred in presence of base (produced by a sequential reaction from the combination of geraniol and farnesol), and it was followed by the desulfonation reaction of the resulting product with LiEt_3BH in presence of $\text{Pd}(\text{dppe})\text{Cl}_2$. Finally, the product in the desulfonation process was subjected for the oxidation with CAN reagent and it produced the final product MK-6 (Figure 19).

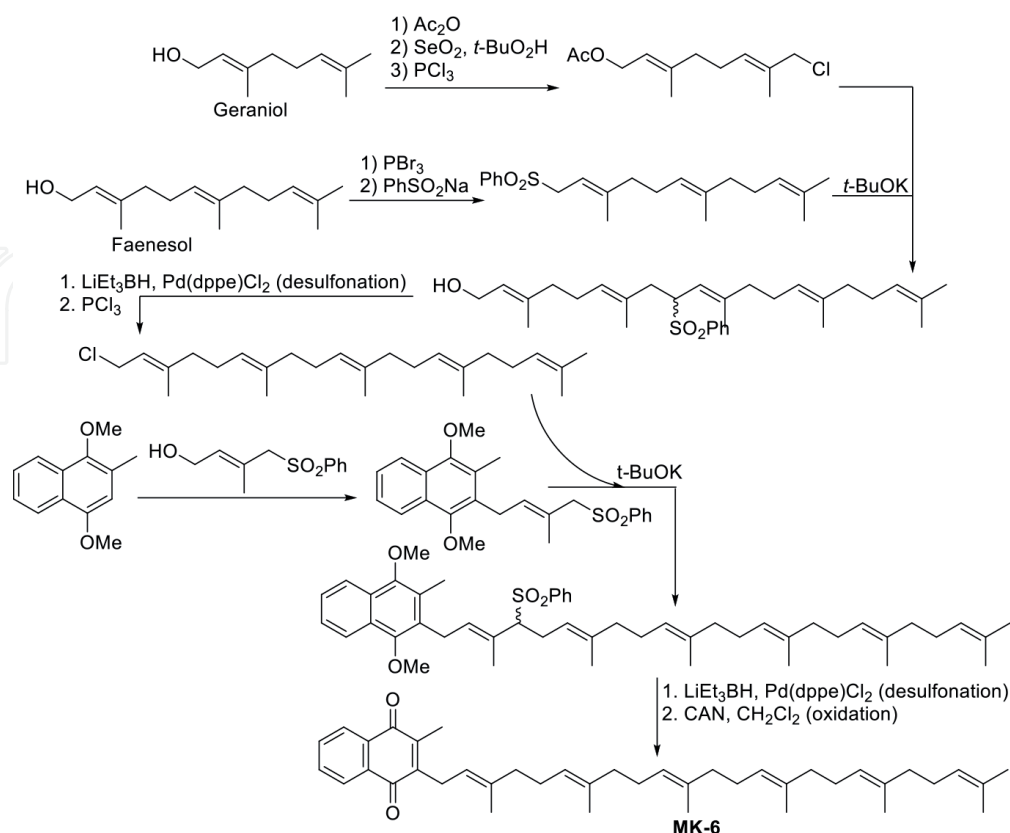


Figure 19.
Convergent synthesis of MK-6.

Lipshutz and group developed a method to introduce a one carbon handle at the C-3 position of menadione molecules and it offered a good synthetic protocol to a wide range of MK-derivatives through a highly probable S_N^2 substitutions and organometallic cross-coupling reactions [55]. The protocol was initiated by the reaction of menadione molecule with formaldehyde and HCl gas, resulting to produce 3-chloromethyl menadione in appreciable yield. The synthesis of vitamin K1 was achieved through the reaction of 3-chloromethyl menadione with phytylalane in presence of $NiCl_2$, Ph_3P and $n-BuLi$. Whereas MK-3 was prepared in the reaction with farnesylalane with *E*-configuration at the coupling position (α -isoprene double bond). The required stereoselective organoalanes [56] were being synthesized by Negishi cross coupling reaction (**Figure 20**).

In the early of 1900s, Saa and group successfully established a protocol by which aldehydes were being used as electrophiles to launch the prenyl side chains in to menadione molecules in the production of MK-2 and MK-4 [57]. During this protocol, bismethyl ether of 2-bromomenadiol undergoes reaction with $n-BuLi$, and generates organolithium reagent through the lithium-bromide ion exchange process. This organolithium reagent attacks on commercially available prenyl aldehydes (citral & geranylgeranial) under BIHY reaction conditions (Birch hydrolysis) produces corresponding benzyl alcohols respectively [58]. The formed alcohol was protected with TMSCl in the presence of HMDS/HMDSZ (hexamethyldisilazane reagent). This protected form of alcohol converted to free methylene group when it reduced in presence of Li & liquid ammonia [59]. The resulting stereochemistry of the α -isoprene double bonds were with more than 95% *E* alkene as presents in

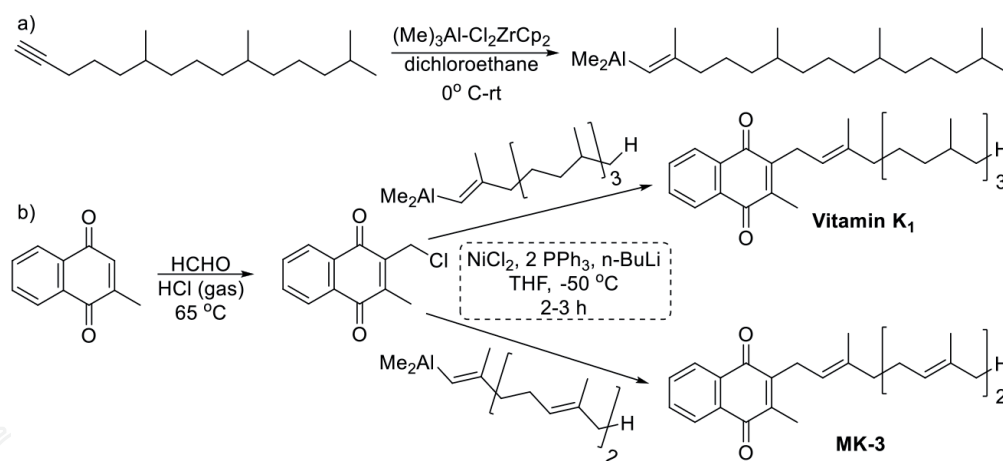


Figure 20.
Synthesis of MK-3 & vitamin K₁ through using phytyl and prenyl organoalane compounds.

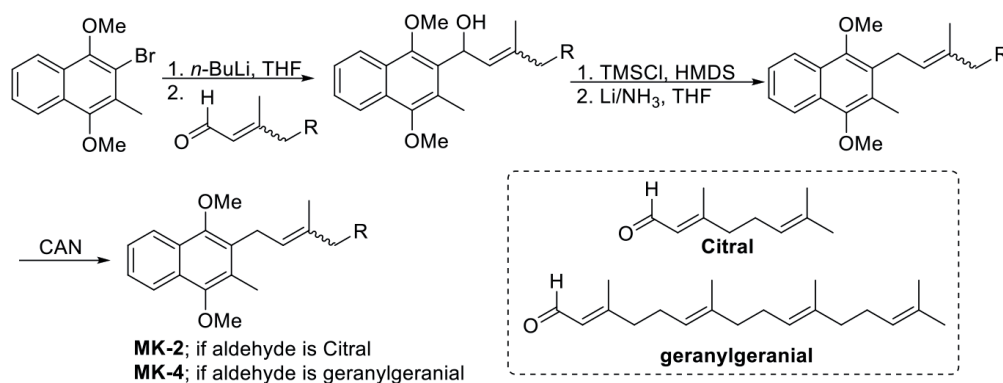


Figure 21.
Synthesis of MK-2 & MK-4 by using birch hydrolysis conditions.

the precursor aldehyde. The methyl ethers of menadione nucleus were removed by CAN to generate MK-2 and MK-4 (**Figure 21**).

4. Brief discussion of vitamin K biology

Biologically these molecules are very important and have been reported for several biomedical purposes. Owing to their severe lipophilicity/ hydrophobicity due to containing multiple isoprene units in the side chain, they are with less solubility and thus causes to difficulties to assess in-vitro studies as these are performed in aqueous solutions. These naphthoquinones have been displayed promising biological activities against tubercular [60, 61], cancer [62–64], cardiovascular [65, 66] and diabetes [67, 68].

In mycobacteria, MenJ (*Rv0561c*) is a highly conserved reductase enzyme demonstrated in mycobacteria knock out strains, and that reduces isoprene units in menaquinones through electron transport, thereby the menaquinones found in mycobacteria are in reduced form (**Figure 22**) [3, 69, 70]. But the ATP levels depends on the total menaquinones present in membrane of bacteria and that facilitated by disruption of MenJ functioning of menaquinone reduction. However, these partially saturated menaquinone's role is unclear in various organisms, but they are found to essential for the growth and survival of pathogenic . The mycobacterial electron transport system is increased by hydrogenation of MK-9, so the survival of the bacteria inside J774A.1 macrophage like cells significantly declined by the deletion of MenJ and that found to be not required for bacterial growth in culture. Thereby, MenJ perhaps identified as a conditional drug target for *Mycobacterium tuberculosis* while in the context of infected macrophage [69].

As a known fact that vitamin K is an essential nutrient that displays potential anticancer properties on a variety of tumor cells [71, 72]. Quinones are the important natural and synthetic molecules as they have considerable biological potential. These compounds display antitumor activity through several mechanism of action. Generally, these molecules have problems with respect to solubility, stability and toxicity. Owing to this reason, these molecules are using as drugs through alternative procedures like controlled-release system of these quinones, and it could be a strategy for improving the pharmacological profile of this class of compounds. Vitamin K mediated mechanisms proceeds to prevent the cell proliferation and growth although unclear, but mostly through oxidative effect and direct arylation of thiols may deplete glutathione and cell cycle arrest. The quinone structure in vitamin k is responsible for the modulation of redox-balance and induction of oxidative stress in cancer cells. The anticancer properties of vitamin K₁ and vitamin K₂ mostly mediated by non-oxidative mechanisms, probably through transcription

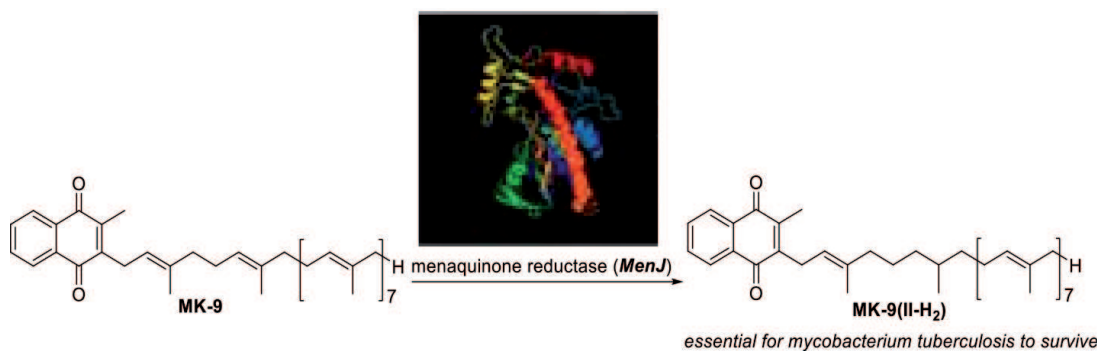


Figure 22.
MenJ reductase reduction transformation of MK-9.

factors, but vitamin K₃ does by reducing oxidative stress and arylation at higher concentrations. It's been evidenced that, bulk doses of vitamin K₂ (2.5 grams given per day) could be safe and not caused to enhancing toxicity levels [73]. Vitamin K₂ also prevents hepatocarcinogenesis in patients with hepatic cirrhosis [74]. Quinones generally undergo one-electron and two-electron reductions, leads to produce semiquinone radicals, as well as hydroquinone's respectively. These factors reduce oxidative stress through the consumption of superoxide radicals and cause to cancer cell homeostasis.

Vitamin K known to reduce complications and improve clinical issues of pre-diabetes and diabetes. Type-2 diabetes mellitus (T2DM) demonstrates when pancreatic β -cells fail to compensate for enduring elevated blood glucose (hyperglycemia) that occurs when glucose uptake in the insulin-sensitive tissues become imbalanced during insulin resistance [75]. Recent clinical trials display T2DM risk reduction was happened with vitamin K supplementation, in addition vitamin K₂ improves insulin sensitivity through the involvement of vitamin K-dependent-protein osteocalcin metabolism and that favors β -cell proliferation, insulin secretion and sensitivity. Vitamin K₂ shows better effect than vitamin K₁ in the context of T2DM [76].

Vitamin K₂ also useful to the bone and cardiovascular related problems. As we know, lower intake of calcium can decrease the bone mineral density, and thus can increase the risk of bone fractures. Although supplemental calcium helps to enhance bone mineral density and strength (prevent osteoporosis), recent evidences informed that higher consumption of calcium supplements may lead to the risk for heart diseases and also can cause to accelerated deposit of calcium in blood-vessel walls and soft tissues. While the vitamin K₂ is related with the inhibition of arterial calcification and arterial stiffening, which means that increased vitamin K₂ intake could be lower the risk of vascular damage as it activates matrix GLA protein (MGP), and that inhibits the deposits of calcium on the walls, and thus reducing the health risks that are associated with calcium levels [77, 78]. The essential component to the synthesis of Gla-protein family is vitamin K and that is very important to the hemostasis as its deficiency causes to acute and dangerous condition due to excessive bleeding.

5. Conclusion

This chapter summarized various synthetic approaches of different variants of vitamin K and their biological application. Although several methods are available, but menadione and its substrate auxiliaries (for example, Diels-Alder adducts, organometallic compounds and others) are the choices to the synthesis of vitamin K's. Their synthesis proceeds through several reactions like, Friedel-Craft alkylation's, condensation reactions, Claisen rearrangement, Diels-Alder reactions and others and by the involvement of nucleophilic and free radical reactions. It also included the information regarding their natural sources. As the huge importance of vitamin K to the mankind, it is being used as food supplementation because it's not produced by mankind. The major dietary source of vitamin K is phyloquinone, which is synthesized by plants and algae. Vitamin K₂ (various forms of menaquinone; MK-4 to MK14), produces from bacteria in the human gut and plays a lesser role in the provision of vitamin K, since it is taken up by the body to only a limited extent. In infants the development of vitamin K is very low, due to its deficiency they are offering vitamin K immediately after the birth and the initial days life. Also incorporated the utility of vitamin K, as its great role in the blood coagulation, in the maintenance of bone health and healthy nervous system, prevention of cardiovascular disease and diabetes.

Menadione, a synthetic product and being used as a pharmaceutical interested molecule. Menaquinone-4 mainly resides in the brain tissues and generates from a tissue-specific transformation of vitamin K. The metabolism of vitamin K is an essential factor to study further vitamin K biology. Further knowledge in this context of vitamin K proved to be beneficial in many areas of science for example like medicine [79].

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Conflict of interest


The authors declare no conflict of interest.

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References

- [1] Kroppenstedt RM, Mannheim W. Lipoquinones in Members of the Family Pasteurellaceae. *Int. J. Syst. Bacteriol.* 1989;39(3):304-308. DOI: 10.1099/00207713-39-3-304.
- [2] Collins MD, Jones D. Distribution of isoprenoid quinone structural types in bacteria and their taxonomic implication. *Microbiol. Rev.* 1981;45(2):316-354.
- [3] Upadhyay A, Fontes FL, Gonzalez-Juarrero M, et al. Partial Saturation of Menaquinone in *Mycobacterium tuberculosis*: Function and Essentiality of a Novel Reductase, MenJ. *ACS Cent. Sci.* 2015;1(6):292-302. DOI: 10.1021/acscentsci.5b00212.
- [4] Vilcheze C, Hartman T, Weinrick B, et al. Enhanced respiration prevents drug tolerance and drug resistance in *Mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci.* 2017;114(17):4495-4500. DOI: 10.1073/pnas.1704376114.
- [5] Nakagawa K, Hirota Y, Sawada N, et al. Identification of UBIAD1 as a novel human menaquinone-4 biosynthetic enzyme. *Nature.* 2010;468(7320):117-121. DOI: 10.1038/nature09464.
- [6] Dunphy PJ, Brodie AF. The structure and function of quinones in respiratory metabolism. In *Methods Enzymology*; Elsevier: Amsterdam, The Netherlands, 1971; 18:407-461.
- [7] Koehn JT, Magallanes ES, Peters BJ, et al. A Synthetic Isoprenoid Lipoquinone, Menaquinone-2, Adopts a Folded Conformation in Solution and at a Model Membrane Interface. *J. Org. Chem.* 2018;83(1):275-288.
- [8] Puffal J, Mayfield JA, Moody DB, Morita YS. Demethylmenaquinone Methyl Transferase Is a Membrane Domain-Associated Protein Essential for Menaquinone Homeostasis in *Mycobacterium smegmatis*. *Front. Microbiol.* 2018;9(3145). DOI: 10.3389/fmicb.2018.03145.
- [9] Conly JM, Stein K. The production of menaquinones (vitamin K2) by intestinal bacteria and their role in maintaining coagulation homeostasis. *Prog Food Nutr Sci.* 1992;16(4):307-43.
- [10] Bentley R, Meganathan R. Biosynthesis of vitamin K (menaquinone) in bacteria. *Microbiol. Rev.* 1982;46(3):241-280. DOI:
- [11] Suvarna K, Stevenson D, Meganathan R, Hudspeth MES. Menaquinone (Vitamin K2) Biosynthesis: Localization and Characterization of the menA Gene from *Escherichia coli*. *J. Bacteriol.* 1998;180(10):2782-2787. DOI: 10.1128/JB.180.10.2782-2787.1998.
- [12] Meganathan R, Kwon. 2009. Biosynthesis of Menaquinone (Vitamin K2) and Ubiquinone (Coenzyme Q). *EcoSal Plus* 3(2):DOI:10.1128/ecosalplus.3.6.3.3.
- [13] Collins MD, Jones D. Distribution of isoprenoid quinone structural types in bacteria and their taxonomic implication. *Microbiol. Rev.* 1981; 45:316-354.
- [14] Cox GB, Gibson F. Biosynthesis of vitamin K and ubiquinone. Relation to the shikimic acid pathway in *Escherichia coli*. *Biochim. Biophys. Acta.* 1964; 93: 204-206.
- [15] Campbell IM, Coscia CJ, Kelsey M, Bentley R. Origin of the aromatic nucleus in bacterial menaquinones. *Biochem. Biophys. Res. Commun.* 1967; 28:25-29.
- [16] Campbell IM. The roles of alanine, aspartate and glutamate in lawsone biosynthesis in *Impatiens balsamina*. *Tetrahedron Lett.* 1969; 1969:4777-4780.
- [17] Robins DJ, Bentley R. Biosynthesis of bacterial menaquinones-evidence for

- the involvement of 2-oxoglutaric acid. J. Chem. Soc. Chem. Commun. 1972; 1972:232-233.
- [18] Kolappan S, Zwahlen J, Zhou R, Truglio JJ, Tonge PJ, Kisker C. Lysine 190 is the catalytic base in MenF, the menaquinone-specific isochorismate synthase from *Escherichia coli*: Implications for an enzyme family. Biochemistry. 2007; 46:946-953.
- [19] Meganathan R. Enzymes from *Escherichia coli* synthesize o-succinylbenzoic acid, an intermediate in menaquinone (vitamin K₂) biosynthesis. J. Biol. Chem. 1981; 256: 9386-9388.
- [20] Palaniappan C, Sharma V, Hudspeth ME, Meganathan R. Menaquinone (vitamin K₂) biosynthesis: evidence that the *Escherichia coli* menD gene encodes both 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylic acid synthase and alpha-ketoglutarate decarboxylase activities. J. Bacteriol. 1992; 174:8111-8118.
- [21] Jiang M, Cao Y, Guo ZF, Chen MJ, Chen XL, Guo ZH. Menaquinone biosynthesis in *Escherichia coli*: Identification of 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylate as a novel intermediate and re-evaluation of MenD activity. Biochemistry. 2007; 46:10979-10989.
- [22] Sieminska EAL, Macova A, Palmer DRJ, Sanders DAR. Crystallization and preliminary X-ray analysis of (1R, 6R)-2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate (SHCHC) synthase (MenD) from *Escherichia coli*. Acta Crystallogr. Sec. F Strut. Biol. Crystal Commun. 2005; 61:489-492.
- [23] Jiang M, Cao Y, Guo ZF, Chen MJ, Chen XL, Guo ZH. Menaquinone biosynthesis in *Escherichia coli*: Identification of 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylate as a novel intermediate and re-evaluation of MenD activity. Biochemistry. 2007; 46:10979-10989.
- [24] Meganathan R, Bentley R. Thiamine pyrophosphate requirement for o-succinylbenzoic acid synthesis in *Escherichia coli* and evidence for an intermediate. J. Bacteriol. 1983; 153: 739-746.
- [25] Bryant RW Jr, Bentley R. Menaquinone biosynthesis: conversion of o-succinylbenzoic acid to 1,4-dihydroxy-2-naphthoic acid and menaquinones by *Escherichia coli* extracts. Biochemistry. 1976;15:4792-4796.
- [26] Shaw DJ, Guest JR, Meganathan R, Bentley R. Characterization of *Escherichia coli* men mutants defective in conversion of o-succinylbenzoate to 1,4-dihydroxy-2-naphthoate. J. Bacteriol. 1982; 152:1132-1137.
- [27] Bentley, R. Molecular asymmetry in biology. Vol. 2. New York: Academic press, Inc.; 1970. p.480-486.
- [28] Baldwin RM, Snyder CD, Rapoport H. Biosynthesis of bacterial menaquinones. Dissymmetry in the naphthalenic intermediate. Biochemistry. 1974; 13:1523-1530.
- [29] Suzuki K, Ueda M, Yuasa M, Nakagawa T, Kawamukai M, Matsuda H. Evidence that *Escherichia coli* ubiA product is a functional homolog of yeast COQ2, and the regulation of ubiA gene expression. Biosci. Biotechnol Biochem. 1994; 58:1814-1819.
- [30] Shineberg B, Young IG. Biosynthesis of bacterial menaquinones: the membrane-associated 1,4-dihydroxy-2-naphthoate octaprenyltransferase of *Escherichia coli*. Biochemistry. 1976; 15:2754-2758.
- [31] Jackman LM, O'Brien IG, Cox GB, Gibson F. Methionine as the source of methyl groups for ubiquinone and vitamin K: a study using nuclear magnetic

resonance and mass spectrometry.
 Biochim. Biophys. Acta. 1967; 141:1-7.

[32] Alison MD, Richard JP, Mark EH, Andrew DA. The Synthesis of Naturally Occurring Vitamin K and Vitamin K Analogues. *Curr. Org. Chem.* 2003; 7(16):1625-1634.

[33] Fieser LF, Campbell WP, Fry EM, Gates MD. Synthetic approach to vitamin K 1. *J. Am. Chem. Soc.* 1939; 61(9):2559-2559.

[34] Binkley SB, Cheney LC, Holcomb WF, et al. The constitution and synthesis of vitamin K1. *J. Am. Chem. Soc.* 1939;61(9):2558-2559.

[35] Almquist HJ, Klose AA. Synthetic and natural antihemorrhagic compounds. *J. Am. Chem. Soc.* 1939;61(9):2557-2558.

[36] Lindlar, H. Patent No. 320582, Switzerland, 1953.

[37] Sato K, Inoue S, Saito K. A new synthesis of vitamin K via π -allylnickel intermediates. *J. Chem. Soc., Perkin Trans. 1.* 1973(0):2289-2293.

[38] Snyder CD, Rapoport H. Synthesis of menaquinones. *J. Am. Chem. Soc.* 1974;96(26):8046-8054.

[39] Evans DA, Hoffman JM. Regiospecific quinone isoprenylation. Examples of remarkably facile [3,3] sigmatropic processes. *J. Am. Chem. Soc.* 1976;98(7):1983-1984.

[40] Chenard BL, Manning MJ, Raynolds PW, Swenton JS. Organocopper chemistry of quinone bisketals. Application to the synthesis of isoprenoid quinone systems. *J. Org. Chem.* 1980;45(3):378-384.

[41] Syper L, Kloc K, Mz.xl, lochowski J. Synthesis of ubiquinone and menaquinone analogues by oxidative demethylation of alkenylhydroquinone ethers with argentic oxide or ceric

ammonium nitrat. *Tetrahedron.* 1980;36(1):123-129.

[42] Maruyama K, Imahori H. Allylation of Quinones via Photoinduced Electron-Transfer Reactions from Allylstannanes. *Bull. Chem. Soc. Jpn.* 1989;62(3): 816-825.

[43] Liebeskind LS, Foster BS. Stannylquinones. Synthesis and utilization as quinone carbanion synthetic equivalents. *J. Am. Chem. Soc.* 1990;112(23):8612-8613.

[44] Tso H-H, Chen Y-J. A convenient one-flask synthesis of vitamin K. *J. Chem. Res. Synop.* 1995;3:104-105.

[45] Mal D, Ghosh K, Jana S. Synthesis of Vitamin K and Related Naphthoquinones via Demethoxycarbonylative Annulations and a Retro-Wittig Rearrangement. *Org. Lett.* 2015;17(23): 5800-5803.

[46] Ryall RP, Nandi DL, Silverman RB. Substituted vitamin K epoxide analogs. New competitive inhibitors and substrates of vitamin K1 epoxide reductase. *Journal of Medicinal Chemistry.* 1990;33(6):1790-1797.

[47] Shearer, M. J. In *Encyclopaedia of Food Science, Food Technology and Nutrition*; Macrae, R., Robinson, R. K., Sadler, M. J., Eds.; Academic Press: London, 1993, p 4804.

[48] Hirschmann R, Miller R, Wendler NL. The Synthesis of Vitamin K1. *J. Am. Chem. Soc.* 1954, 76, 4592-4594.

[49] Schmida R, Antoulas So, RÃ ttimann A, Schmid M, Vecchi M, Weiserb H. Synthesis of All Four Stereoisomers of (E)-Vitamin KT (Phylloquinone), Analysis of Their Diastereoisomeric and Enantiomeric Purities and Determination of Their Biopotencies. *Helv. Chim. Acta* 1990;73(5):1276-1299.

[50] Jacobsen N, Torssell K. Radikalische Alkylierung von Chinonen: Erzeugung

- von Radikalen in Redoxreaktionen. Liebigs Ann. Chem. 1972;763(1):135-147.
- [51] Yamago S, Hashidume M, Yoshida J-i. A new synthetic route to substituted quinones by radical-mediated coupling of organotellurium compounds with quinones. Tetrahedron. 2002;58(34): 6805-6813.
- [52] Rüttimann, A. Recent Advances in the Synthesis of K-Vitamins. Chimia 1986, 40, 290-306.
- [53] Yerramsetti N, Dampanaboina L, Mendu V, Battula S. Synergistic factors ensue high expediency in the synthesis of menaquinone [K2] analogue MK-6: Application to access an efficient one-pot protocol to MK-9. Tetrahedron.76(49):131696.
- [54] Baj A, WaÅ,ejko P, Kutner A, Kaczmarek Åu, Morzycki JW, Witkowski Sa. Convergent Synthesis of Menaquinone-7 (MK-7). Org. Process Res. Dev. 2016;20(6):1026-1033.
- [55] Lipshutz BH, Kim SK, Mollard P. An Expeditious Route to COQn, Vitamins K1 and K2, and Related Allylated para-Quinones Utilizing Ni(0) Catalysis. Tetrahedron 1998;54:1241-1253.
- [56] Negishi E, Van Horn DE, Yoshida T. Controlled carbometalation. 20. Carbometalation reaction of alkynes with organoalene-zirconocene derivatives as a route to stereo- and regiodefined trisubstituted alkenes. J. Am. Chem. Soc. 1985; 107:6639-6647.
- [57] Garcias X, Ballester P, Capo M, Saá JM. 2.DELTA.-Stereocontrolled Entry to (E)- or (Z)-Prenyl Aromatics and Quinones. Synthesis of Menaquinone-4. J. Org. Chem. 1994; 59:5093-5096.
- [58] Ballester P, Capo M, Garcias X, Saá JM. Synthesis of prenylated quinones by the oxidative degradation approach. Birch vs vinylogous Birch hydrogenolysis (BIHY vs VIBIHY) in controlling 2.DELTA. stereochemistry of the prenyl chain. J. Org. Chem. 1993; 58:328-334.
- [59] Ballester, P.; Saá, J.; Capo, M. Prenylation of Aromatics. Lithium-Ammonia Reduction of O-Silylated Tertiary Cinnamyl Alcohols. Tetrahedron Lett. 1990, 31, 1339-1342.
- [60] Gengenbacher M, Kaufmann SHE. Mycobacterium tuberculosis: success through dormancy. FEMS Microbiol. Rev. 2012;36(3):514-532. DOI: 10.1111/j.1574-6976.2012.00331.x.
- [61] Bahuguna A, Rawat DS. An overview of new antitubercular drugs, drug candidates, and their targets. Med. Res. Rev. 2020;40(1):263-292. DOI: 10.1002/med.21602.
- [62] Vitor Francisco F, Caroline Deckmann N, Patricia Garcia F, Debor Omena F, Fernando de Carvalho da S. Strategies for Increasing the Solubility and Bioavailability of Anticancer Compounds: β -Lapachone and Other Naphthoquinones. Curr. Pharm. Des. 2016;22(39):5899-5914. DOI: 10.2174/1381612822666160611012532.
- [63] Setoguchi S, Watase D, Matsunaga K, et al. Enhanced antitumor effects of novel intracellular delivery of an active form of menaquinone-4, menahydroquinone-4, into hepatocellular carcinoma. Cancer Prev Res (Phila). 2015;8(2):129-138. DOI: 10.1158/1940-6207.CAPR-14-0292.
- [64] Dasari S, Ali SM, Zheng G, et al. Vitamin K and its analogs: Potential avenues for prostate cancer management. Oncotarget. 2021/01/29 2017;5(0):57782-57799. DOI: 10.18632/oncotarget.17997.
- [65] Ingles DP, Cruz Rodriguez JB, Garcia H. Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment. Curr Cardiol Rep. 2020;22(4):22. DOI: 10.1007/s11886-020-1270-1.

- [66] Maresz K. Proper Calcium Use: Vitamin K2 as a Promoter of Bone and Cardiovascular Health. *Integra Med* (Encinitas, Calif.). 2015;14(1):34-39.
- [67] Karamzad N, Maleki V, Carson-Chahhoud K, Azizi S, Sahebkar A, Gargari BP. A systematic review on the mechanisms of vitamin K effects on the complications of diabetes and pre-diabetes. *BioFactors*. 2020;46(1):21-37. DOI: 10.1002/biof.1569.
- [68] Li Y, Chen JP, Duan L, Li S. Effect of vitamin K2 on type 2 diabetes mellitus: A review. *Diabetes Res Clin Pract*. 2018;136:39-51. DOI: 10.1016/j.diabres.2017.11.020.
- [69] Kumar S, Koehn JT, Gonzalez-Juarrero M, Crans DC, Crick DC. Mycobacterium tuberculosis Survival in J774A.1 Cells Is Dependent on MenJ Moonlighting Activity, Not Its Enzymatic Activity. *ACS Infect. Dis*. 2020;6(10):2661-2671. DOI: 10.1021/acsinfecdis.0c00312.
- [70] Upadhyay A, Kumar S, Rooker SA, et al. Mycobacterial MenJ: An Oxidoreductase Involved in Mena-quinone Biosynthesis. *ACS Chem. Biol*. 2018;13(9):2498-2507. DOI: 10.1021/acscchembio.8b00402.
- [71] Wang Z, Wang M, Finn F, Carr BI. The growth inhibitory effects of vitamins K and their actions on gene expression. *Hepatology*. 1995;22(3):876-882. DOI:
- [72] Sata N, Klonowski-Stumpe H, Han B, Häussinger D, Niederau C. Menadione Induces Both Necrosis and Apoptosis in Rat Pancreatic Acinar AR4-2J Cells. *Free Radical Biology and Medicine*. 1997;23(6):844-850. DOI: 10.1016/S0891-5849(97)00064-6.
- [73] Margolin KA, Akman SA, Leong LA, et al. Phase I study of mitomycin C and menadione in advanced solid tumors. *Cancer Chemother Pharmacol*. 1995;36(4):293-298. DOI: 10.1007/BF00689046.
- [74] Tamori A, Habu D, Shiomi S, Kubo S, Nishiguchi S. Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma. *Hepatol Res*. 2007;37(Suppl 2):S303-307.
- [75] Karamzad N, Maleki V, Carson-Chahhoud K, Azizi S, Sahebkar A, Gargari BP. A systematic review on the mechanisms of vitamin K effects on the complications of diabetes and pre-diabetes. *BioFactors* 2019; 46(1):21-37.
- [76] Aguayo-Ruiz JI, García-Cobián TA, Pascoe-González S, Sánchez-Enríquez S, Llamas-Covarrubias IM, García-Iglesias T, López-Quintero A, Llamas-Covarrubias MA, Trujillo-Quiroz J, Rivera-Leon EA. Effect of supplementation with vitamins D3 and K2 on undercarboxylated osteocalcin and insulin serum levels in patients with type 2 diabetes mellitus: a randomized, double-blind, clinical trial. *Diabetol Metab Syndr* 2017; 12(1):73.
- [77] Maresz K. Proper Calcium Use: Vitamin K2 as a Promoter of Bone and Cardiovascular Health. *Integr Med* (Encinitas). 2015;14(1):34-39.
- [78] van Ballegooijen AJ, Beulens JW. The Role of Vitamin K Status in Cardiovascular Health: Evidence from Observational and Clinical Studies. *Curr Nutr Rep*. 2017;6(3):197-205.
- [79] Card DJ, Gorska R, Cutler J, Harrington DJ. Vitamin K metabolism: current knowledge and future research. *Mol Nutr Food Res*. 2014 58(8): 1590-1600.